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10/719,007	11/20/2003	Randolph Mellus Johnson	DURE-007CON2	9101
24353 7590 06/02/2009 BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			EXAMINER GHALI, ISIS A D	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/719,007	Applicant(s) JOHNSON ET AL.	
	Examiner Isis A. Ghali	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 48-56, 58-67, 69-72, 74-81, 83-94 and 96-99 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 48-56, 58-67, 69-72, 74-81, 83-94 and 96-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/19/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The receipt is acknowledged of applicants' amendment and IDS, both filed 03/19/2009.

Claims 57, 68, 73, 82, and 95 have been canceled by "Examiner Amendments" dated 06/27/2008.

Claims 48-56, 58-67, 69-72, 74-81, 83-94, 96-99 are pending and included in the prosecution.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 48-56, 58-67, 69-72, 74-81, 83-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sufentanil as a fentanyl congener delivered by subcutaneous Duros pump and delivered at a delivery rate of 2.5, 5, 7.5, 10 and 20 µg/hr at low volume rate of 0.056 µl/hr (1.4 µl/day), does not reasonably provide enablement for fentanyl itself and any other fentanyl congener delivered by implantable convective delivery device. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir.1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention is a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject wherein the composition is administered to the subject using an implantable convective delivery system for 48 hours or more in certain concentration delivered at specific delivery volume rate from the implantable convective device. Nowhere in the specification had applicants showed treating pain using fentanyl or fentanyl congener other than sufentanil.

The breadth of the claims: The claims are broad. The claims encompass fentanyl and all its available congeners, and any congeners that may further to come in the future. Fentanyl and its congeners differ in their potency and consequently effective doses and period of action. The claims recite "a congeners" that can be any congener. The claims as interpreted in light of the specification are broad because in page 16 of the present specification applicants stated that: "Exemplary fentanyl congeners include,

but are not necessarily limited to sufentanil, alfentanil, lofentanil, carfentanil'

remifentanil, trifentanil, and mirfentanil." Therefore, applicants' disclosure does not limit the fentanyl congeners. Further the claimed concentrations and delivery rates are very broad, and it is not clear which concentration belongs to which congener.

The state of the prior art: The state of the recognized that fentanyl and its congeners have different pharmacokinetics and delivered in different doses to obtain the analgesic effect. The article "Clinical Pharmacokinetics of Alfentanil, Fentanyl and Sufentanil", by Scholz et al., provided by applicants in IDS filed 06/20/2006, disclosed that pharmacokinetics of opioid analgesics are affected by several factors including patient age, plasma protein content, acid-base status, and cardio-pulmonary bypass, see summary and pages 281-284. The article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al. at table 1, demonstrated that fentanyl and its congener have different lipid solubility and half life, plasma clearance, etc., and these variations will provide variations in their route of delivery, effective doses, duration of action, and analgesia they provide. Not all fentanyl and its congeners that encompassed by the claims can be delivered by the same composition in the same concentration and delivery rates and not all expected to provide the same effect.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on treating pain by implantable convective device comprising fentanyl and its congeners at a concentration of 0.5-500 mg/ml delivered at rate from about 0.01 μ l/hr to about 2 ml/hr. The specification describes

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sufentanil delivered by subcutaneous implantable convective device DUROS comprising sufentanil delivered at a delivery rate of 2.5, 5, 7.5, 10 and 20 $\mu\text{g/hr}$ at low volume rate of 0.056 $\mu\text{l/hr}$ (1.4 $\mu\text{l/day}$) (examples 2 and 5). Examples 3 shows formulations comprising sufentanil in benzyl alcohol in an amounts 397 mg/ml and 310 mg/ml. Example 4 shows formulations comprising sufentanil in polysorbate 20 and benzyl benzoate in an amount 248 mg/ml and 77 mg/ml. However, it is not clear that examples 3 and 4 are delivered by implantable convective device. In page 6 of the present specification, second paragraph, applicants disclosed that the delivery rate of sufentanil is "from about 0.01 $\mu\text{g/hr}$ or 0.1 $\mu\text{g/hr}$, 0.25 $\mu\text{g/hr}$, 1 $\mu\text{g/hr}$, generally up to about 200 $\mu\text{g/hr}$ ". It is not obvious from the disclosure of sufentanil by subcutaneous implantable convective device at specific concentration delivered at specific rate if fentanyl and the other congeners will work for treating pain if delivered in the same devices at the same concentration and at the same delivery rate. Wappler et al. disclosed that sufentanil is more potent than fentanyl and its congeners and showed that fentanyl and its congeners have different pharmacokinetics. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope

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of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to treating pain with fentanyl and congeners, other than sufentanil, using implantable convective device loaded with the claimed wide range of amount and delivered at the wide range volume delivery rate, makes practicing the claimed invention unpredictable in the terms of concentration and delivery rates of fentanyl and all its congeners to provide systemic analgesia for at least 48 hours.

The presence or absence of working examples: The specification exemplified only sufentanil is specific doses and delivery rates. No working examples to show using fentanyl or any other congeners. Therefore, the specification has enabled using sufentanil to treat pain by providing systemic analgesia in specific concentrations and delivery rates delivered from implantable convective devices.

The quantity of experimentation necessary: The art demonstrates that sufentanil is more potent and has pharmacokinetics that differ from fentanyl and its other congeners. The specification disclosed only sufentanil at specific concentrations and delivery rates. Therefore, the practitioner would turn to trial and error experimentation to practice the instant method for treating pain using fentanyl or other congeners, other than sufentanil, without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

Response to Arguments

3. Applicant's arguments filed 03/19/2009 have been fully considered but they are not persuasive.

Applicants argue that the application as filed enables the delivery of a composition comprising fentanyl or a fentanyl congener such as sufentanil according to the claimed methods. At page 19 of the application as filed, the specification describes fentanyl or fentanyl congener formulations. The specification does not limit the described formulations to sufentanil, but instead provides sufentanil as an exemplary fentanyl congener which may be formulated in the manner described. Applicants argue that the specification describes specific implantation and delivery sites which may be used in connection with the claimed methods, specific delivery periods, specific low volume rates of delivery, and specific delivery devices compatible with the delivery of fentanyl or fentanyl congener formulations. The specification also describes specific methods by which a physician can select an appropriate dose of a fentanyl or fentanyl congener formulation for use according to the claimed methods (Example 1). Applicants further argue that the specification describes exemplary loading parameters for an implantable convective delivery system (Example 2), specific formulations of an exemplary fentanyl congener (sufentanil) comprising benzyl alcohol or benzyl benzoate (Examples 3-4), and an in-vitro method of testing the release profile of fentanyl or a fentanyl congener from an implantable convective delivery system (Example 5). Thus, in view of this disclosure, one of ordinary skill in the art could have readily practiced the claimed methods using fentanyl itself or fentanyl congeners as described in the

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specification. Applicants argue that the level of experimentation required to practice the full scope of the claimed methods would not be undue.

In response to these arguments, it is argued that under 112 enablement requirements, it is required partial or complete disclosure of reasonable number of fentanyl congeners at delivery rate encompassed by the claims suitable to practice the claimed method in order to convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter. The claims neither provide those delivery rate and doses of congeners that are known to have different pharmacokinetics and require different dose regimen to practice the inventions, nor “inform the public” during the life of the patent of the limits of the monopoly asserted. “A fentanyl congener” could encompass all known and unknown fentanyl congeners, and applicants claims represents only an invitation to experiment regarding possible congeners and their doses and delivery rates to provide pain relief for the claimed periods. The present specification directed to “sufentanil DUROS implantable pump”, examples 2 and 5 of the present specification. In page 16 of the present specification applicants stated that: “Exemplary fentanyl congeners include, **but are not necessarily limited to** sufentanil, alfentanil, lofentanil, carfentanil, remifentanil, trifentanil, and mirfentanil.” Example 1 that applicant alleged to teach other fentanyl congeners, teaches only sufentanil. Therefore, applicants’ disclosure does not limit the fentanyl congeners. Further, examples 3 and 4 are not directed to implantable convective devices as instantly claimed. Applicant disclosed sufentanil delivered by convective devices in examples 2 and 5 and only at

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specific delivery rates of 2.5, 5, 7.5, 10 and 20 µg/hr at low volume rate of 0.056 µl/hr (1.4 µl/day).

Accordingly, it is the examiner's duty to determine exactly what subject matter is encompassed by the claims. See, *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003). The present specification enabled sufentanil implantable devices that provides specific delivery rate of sufentanil. Nowhere applicants have disclosed delivery rates of any other fentanyl congeners. The claims encompass all fentanyl congeners. It is not clear from the disclosure of implantable devices having sufentanil in specific formulation and concentration, if all fentanyl congeners that vary in their pharmacokinetics will provide analgesia if delivered in the same delivery rates in the same amounts for the same periods of times as sufentanil.

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993). The instant specification does not teach how to make or use the full scope of the broad claimed "fentanyl and a fentanyl congener". Applicants do not need to describe in writing all embodiments suitable for the practice of a claimed invention, however, the disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the limitations fall within the scope of a claim will possess the alleged activity.

Additionally, the claims are broad, and the examiner's concern is that the scope of enablement provided to one skilled in the art by the disclosure is not commensurate

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with the scope of protection sought by the claims. Applicants did not show possession of the invention as instantly claimed with all its limitations, by any means of descriptive words, structure, figures, or diagrams. The specification has thus not met the requirements of first paragraph of 35 USC 112, which states that: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention".

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 56, 67, 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The expression "at least about" in each of the claims renders the claims indefinite because the expression "at least" and the term "about" contradict each other. The expression "at least" limits the claim to value equal or more than the recited value following the expression "at least", on the other hand, the term "about" broadens the recited value to encompass values below the recited value. Therefore, the claims are indefinite. Recourse to the specification, does not define the tem or expression.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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9. Claims 48-56, 58-67, 69-72, 74-81, 83-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al. combined with article "Long term spinal therapy in terminally ill cancer patients" by Wagemans et al., Peterson et al. (US 6,524,305) and Nelson et al. (US 5,980,927).

Applicants claim

Currently amended claim 48 recites: a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject, wherein the fentanyl or fentanyl congener is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system for 48 hours or more at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

Currently amended claim 63 recites a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or a fentanyl congener, wherein said fentanyl or fentanyl congener is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

Currently amended claim 84 recites a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising fentanyl or fentanyl congener, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate from about 0.1 $\mu\text{l/day}$ to about 2 ml/day and is sufficient to deliver from about 0.01 $\mu\text{g/hour}$ to about 200 $\mu\text{g/hour}$ of the fentanyl or fentanyl congener to the subject, and further wherein said amount of delivered fentanyl or fentanyl congener is sufficient to establish a systemic analgesic effect in the subject.

Determining the scope and contents of the prior art (MPEP § 2141.01)

Wappler teaches that the administration of sufentanil is suitable for intensive care patients for systemic sedation and analgesia without significant respiratory depression during spontaneous breathing. Sufentanil continuous infusion was provided in a dose between 0.075 to 2.5 $\mu\text{g/kg/hr}$ with median of 0.6 $\mu\text{g/kg/hr}$. See 1st, 2nd and 5th pages of the translation. For the average person weighing 60 kg, the dose disclosed by Wappler that induces systemic analgesia will ranges from 4.5 $\mu\text{g/hr}$ to 150 $\mu\text{g/hr}$, which is 98-3600 $\mu\text{g/day}$, i.e. 0.098 to 3.6 mg/day. Present claims 48 and 63 recite 0.5-500 mg/ml, and teaches from 0.01 $\mu\text{l/day}$ to 2 ml/day. This means if average of 250.25 mg delivered at the lowest delivery rate of 0.01 $\mu\text{l/day}$, then low delivery rate as low as 0.0025 mg/day to 1000 mg/day if delivery rate is 2 ml/day, i.e. 2.5-1000,000 $\mu\text{g/day}$. Present claim 84 recites 0.01 $\mu\text{g/hour}$ to about 200 $\mu\text{g/hour}$. Therefore, the claimed delivery rates of

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sufentanil are taught by the reference, and the claimed delivery rates disclosed by the reference falls within the broad claimed delivery rates.

Although Wappler teaches the same sufentanil delivery rates as the instantly claimed, however the reference does not teach delivery of sufentanil using implantable convective devices that deliver from 0.01 $\mu\text{l/day}$ to 2ml/day to provide analgesia for prolonged periods.

Wagemans et al. teach long-term opioid therapy with minimal side effects and efficacy throughout the body and for different types of pain, i.e. systemic, with sufentanil preferred analgesic (see the entire document, especially the abstract). The analgesia is achieved by systemic absorption of the opioid (page 72, left column, last paragraph). The opioid is administered in its minimal effective dose (table 2, page 72). The analgesic is administered by implanted infusion pump for months or years and provides constant infusion rate (page 73, left column, second paragraph). The reference further suggested physician can manage the patient's analgesic requirement (page 73, right column, last paragraph).

Peterson teaches implantable osmotic delivery system flow modulator assembly (convective device) that enhances performance of implantable osmotic devices and reduced the amount of wasted beneficial agents (abstract; col.3, lines 63-65; col.4, lines 19-20; col.11, lines 26-28; col.12, lines 38-42). The delivery system provides flow of beneficial agent between 0.02 to 50 $\mu\text{l/day}$ and suitable to deliver analgesics (col.11, lines 20-23; col.13, line 65). Table I shows pumping of the beneficial agents in mg/day and amount delivered for year.

Nelson teaches prolonged delivery of sufentanil by implanted devices over periods extends up to one year (abstract; col.2, lines 39-41). Table I of the reference teaches that loading dose sufficient for long period administration, e.g. six month dose, can be calculated if the daily dose is known. Nelson teaches the daily dose of sufentanil is 0.1 to 0.3 mg/day (col.6, lines 26-31).

Ascertaining the differences between the prior art and the claims at issue
and resolving the level of ordinary skill in the pertinent art (MPEP §
2141.012)

Therefore, at the time of the invention, it was well known to administer sufentanil in a continuous manner at a daily dose of 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day, to induce analgesia as taught by Wappler. It was further known that sufentanil is the preferred analgesic for long-term opioid therapy and can be administered in the minimal effective dose for months or years by implantable pumps as taught by Wagemans. Wagemans further suggested physician can manage the patient's analgesic requirement.

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered continuously at concentration of 4.5 µg/hr to 150 µg/hr, i.e. 98-3600 µg/day, as disclosed by Wappler and deliver sufentanil using implantable infusion pump disclosed by Wagemans. One would have been motivated to do so because Wagemans teaches that implanted infusion pump is suitable for long term opioid delivery and can delivers

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sufentanil for months or years and provides constant infusion rate, as presently claimed. One would have reasonably expected success of providing continuous analgesia for prolonged period of times up to years with delivery rate of sufentanil from 4.5 $\mu\text{g/hr}$ to 150 $\mu\text{g/hr}$.

Further, because both of Wappler and Wagemans recognized that delivery of continuous analgesia for long time was demanded, and Wagemans suggested implanted infusion pump for prolonged delivery of small dose. Therefore, one having ordinary skill in the art at the time of the invention would have been motivated to use the implantable pump disclosed by Peterson because Peterson shows that implantable osmotic delivery system can deliver active agent including analgesics for years at a low rate of 0.02 to 50 $\mu\text{l/day}$ with enhanced-performing implantable osmotic devices and with reduction of the waste of beneficial agent. One would have reasonably expected inducing analgesia using implanted infusion pump that delivers low rate loaded with minimal analgesic dose of sufentanil that delivers 98-3600 $\mu\text{g/day}$ from pump that provides low rate of delivery of 0.02 to 50 $\mu\text{l/day}$ for long time. Therefore, at the time of the invention, applicant claim low delivery rates between 0.01 $\mu\text{l/day}$ to 2ml/day, which is the selection of the delivery rate taught by Peterson.

Additionally, one having ordinary skill in the art would have been able to calculate the analgesic dose of sufentanil delivered from implantable device as disclosed by Nelson. Nelson disclosed that the sufentanil dose is from 0.1 mg/day to 0.3 mg/day, and showed that it is possible to calculate the dose to be loaded in an implantable device if the daily dose and period of administration are known.

Therefore, at the time of the invention, one skilled in the art would be motivated to induce analgesia using the present method because the prior art teaches the use of sufentanil for prolonged delivery at minimal doses, and further at low delivery rates from implantable devices.

All the elements of the claimed method were known at the time of the invention and further the cited references provided motivation to combine them. It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.*, 425 U.S. 273,282 (1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions."

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103(a).

Response to Arguments

10. Applicant's arguments filed 03/19/3009 have been fully considered but they are not persuasive.

Applicants argue that the proposed combination of Wappler with Wagemans fails to teach or suggest each and every claim element. Wappler teaches continuous infusion

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of sufentanil at a dose of 4.5 µg/hr to 150 µg /hr and that Wagemans teaches long-term opioid therapy with minimal side effects and efficacy throughout the body for different types of pain. The combination of Wappler and Wagemans fails to teach or suggest at least the following element "the composition is delivered from the system for 48 hours or more at a low volume rate from about 0.01 µl/day to about 2 ml/day and is sufficient to deliver from about 0.01 µg /hour to about 200 µg /hour of the sufentanil to the subject."

In response to this argument, the argument rendered moot in view of the new ground of rejection because the Peterson teaches the low delivery volume rate for long time. The implantable devices that deliver low volume for extended periods were known at the time of the invention and taught by Peterson. Further Peterson suggested delivery of analgesics, and Wagemans desired long term opioid therapy. Therefore, at the time of the invention, one having ordinary skill in the art would have used the implantable osmotic device disclosed by Peterson to deliver sufentanil in the doses disclosed by the combination of Wappler and Wagemans. Nelson supports the teaching of Wappler regarding the dose of sufentanil, and further showed that is possible to calculate the required does of sufentanil to be loaded in implantable device for long term therapy.

Applicants argue that no apparent reason for one skilled in the art to combine the disclosed delivery rates of Wappler in a continuous infusion method as described by Wagemans. This is because Wagemans solves the problem of providing analgesia in a subject in a completely different manner than that employed by Wappler. Wagemans

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describes spinal, i.e., local administration of opioids, to act directly at the spinal cord level by binding to specific opioid receptors in the dorsal horn of the spinal cord.

Wagemans does not teach or suggest systemic administration of sufentanil as currently claimed, because to do so would defeat Wagemans purpose of providing analgesia via local administration to the spine. Wappler does not explicitly indicate the route of administration used. However, Wappler does suggest that the drug is delivered intravenously, i.e., systemically.

In response to this argument, the present claims are directed to method of inducing systemic analgesia and recite only one step of the method, which is administration of sufentanil, and no specific route of administration is recited.

Wagemans teaches long-term opioid profound therapy, i.e. not only at the site of administration, with minimal side effects and efficacy throughout the body and for different types of pain, and further teaches sufentanil is a preferred analgesic in minimal effective dose. Wagemans teaches systemic absorption of opioids delivered by epidural and intrathecal routes, page 72, right column, first full paragraphs. Additionally, Wagemans teaches delivery by implanted infusion pump for months or years and provides constant infusion. Therefore, constant infusion for long periods of minimal effective dose of sufentanil for systemic effect is taught by Wagemans. Wappler disclosed continuous pump infusion. Wappler is relied upon for teaching the doses. Both Wagemans and Wappler teach method of delivery of sufentanil by infusion and both teach systemic delivery, however, Wappler preferred intravenous infusion and Wagemans preferred spinal infusion. The present claims are not directed to any specific

site of delivery of sufentanil. The disclosed examples and preferred embodiment do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Applicants argue that the proposed combination fails to render the claims prima facie obvious.

In response to this argument, it is argued that the present claimed method as a whole is taught by the combination of the cited prior art as currently rejected. Therefore, the invention as a whole is taught by the combination of the cited prior art. A prima facie case of obviousness has been established.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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/Isis A Ghali/
Primary Examiner, Art Unit 1611

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